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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,099	03/31/2004	Katalin Varadi	P-279.00	9454

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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
06/23/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/816,099	VARADI ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-13,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-13,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 18, 2009 has been entered. Claims 1 and 22 have been amended. Claims 9, 14-21 and 24 have been canceled. No claims have been added. Accordingly, claims 1-8, 10-13, 22 and 23 are examined on the merits herewith.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is between step (b) and step (c) in claim 22, that the mixture of the sample, the lyophilized TF/PL complex, and the lyophilized combination of thrombin substrate plus calcium chloride plus DMSO are mixed to dissolve the solid components (in particular the TF and the thrombin substrate), so that thrombin generation can occur and its activity measured. The "wherein" clauses in claim 22 step (a) are possible uses or

intended uses of the lyophilized substrate-$CaCl_2$-DMSO mixture, but they are not assay steps. Appropriate correction is required.

Claim Rejections - 35 USC § 103

Claims 1-8, 10-13, 22 and 23 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Wöber et al. (US 6,124,110) in view of Hawkins et al. (US 5,625,036), Lawson et al. ("The evaluation of complex-dependent alterations in human Factor VIIa*," J Biol Chem 267(7):4834-4843, 1992), Váradi et al. ("Monitoring the bioavailability of FEIBA with a thrombin generation assay," J Thrombosis and Heamostasis 1:2374-2380, 2003), Chan (US 5,952,198), Hogan et al. (US 6,074,826), Weinstein et al. (US 6,576,422) and Dubrow et al. (US 6,756,019), and further in view of Dou et al. (US 2002/0151582) and CRC (CRC Handbook of Chemistry and Physics 51st Ed., R.C. Weast, ed., The Chemical Rubber Co., Cleveland, 1970, p. B-77). This rejection has been discussed in the previous Office actions.

As previously discussed, Applicants assert that the claimed invention is not obvious, because Applicants have an unexpected result. This result is that lyophilizing a mixture comprising a fluorescently labeled thrombin substrate and calcium chloride together significantly improves the solubility of the substrate in aqueous solution relative to lyophilizing these two components separately, or lyophilizing the substrate without the calcium chloride, for subsequent dissolution in a calcium chloride solution. Applicants have presented results from an experiment showing that when a solution of the fluorescently labeled thrombin substrate, in DMSO and water, is lyophilized, and, when resolubilization in a calcium chloride solution is attempted, the substrate is difficult to dissolve, and constant stirring and heating are required (sample 1 in Table 1). But, when a solution of the substrate and calcium chloride in DMSO and water is lyophilized, the substrate can be easily redissolved by adding water or a buffer. The

buffering ingredients may be in the substrate solution before lyophilization or they may added when the substrate is redissolved after lyophilization (samples 3a, 3b and 4). Applicants have presented photographs showing the differences among the samples.

The higher-quality photographs provided to Examiner on June 1, 2009 do show that the sample from Experiment 1a is a clear solution with a precipitate at the bottom of the vial. The sample vials from Experiments 3a and 3b show clear solutions with no precipitate.

In reply however, as previously discussed, Applicants arguments' and Applicants' data are not persuasive, because the claimed kit, and the method of its use, appear to be that used by Váradi et al. to measure thrombin generation time (see p. 2375, right col.). In the assay of Váradi et al., for each assay sample, 10 µl of TF/PL solution is added to 50 µl of a solution containing 1 mM thrombin substrate and 15 mM calcium chloride. 40 µl of plasma is then added to start the reaction. Váradi et al. do not disclose how the substrate solution is made. But, there is no indication that this solution is cloudy, or prone to precipitation, or that it requires special treatment or presents particular problems in carrying out the assay. Particularly as fluorescence of the cleaved substrate is measured, not light transmission, there is no indication that any cloudiness in the assay samples that might occur is a problem. Thus, it is not clear that Applicants' alleged advantage is an advantage over the prior art.

Moreover, this solution need not have been made in the way that Applicants' sample 1 was made, by reconstituting a lyophilized preparation of thrombin substrate in a 15 mM aqueous solution of calcium chloride. The assay reagent of Váradi et al. could have been made by mixing a concentrated solution of the thrombin substrate in 10% DMSO in water (for example, a 10 X solution, a 10 mM stock solution) with a concentrated solution of calcium chloride (for example, a 10 X solution, 150 mM stock solution) and eight parts of water. It is not clear that, in the prior art, assay reagents were prepared as in Applicants' sample 1.

Based on the specification, the aforementioned results do not appear to be Applicants' point of novelty. What the specification discloses is that the claimed kit has the advantages that it provides a simple, fast and reproducible assay, one that is more efficient that previous assays (see paragraph 10).

Additionally, the Declaration does not serve to overcome the rejection, because is not commensurate with the scope of the claims. Applicants tested only one species of the genus of thrombin substrates, yet assert that their results apply to the entire genus.

Regarding amended claims 1 and 22, the specification does not disclose that Applicants lyophilized an aqueous solution of only calcium chloride, DMSO and the thrombin substrate for the “lyophilized mixture.” Example 6 of the specification, which may be prophetic, discloses that the substrate Z-Gly-Gly-Arg-AMC/HCl dissolved in HEPES with NaCl and DMSO is stirred, calcium chloride is added, and a precipitate forms. The Example discloses that the mixture is diluted in the same buffer and then frozen or lyophilized to yield a "ready to use" solution, upon reconstitution with water. The specification does not state that reconstitution results in a clear solution, just a "ready to use solution." As the solution before lyophilization had to be vigorously mixed to dissolve the precipitate, it is not apparent how a clear solution forms when water is added to the lyophilized mixture.

Regarding the last paragraph of Applicants' Remarks filed on May 18, 2009, that Applicants' improved result would be expected with serum as a substrate diluent as well as with water, Examiner's point was not that water and serum could not yield a similar result. Examiner's point was that, as noted above, the "wherein" clauses in claim 22 are not required method steps. These wherein clauses are intended or potential uses of the lyophilized thrombin substrate-calcium chloride-DMSO mixture, a mixture that can be dissolved in water to prepare an assay reagent.

In view of the foregoing, the rejection of record is maintained.

No claim is allowed.

Art of Record

Kakkar et al. (US 6,337,881 B1)) disclose a large variety of chromogenically labeled thrombin substrates and inhibitors based on tripeptides that have affinity for the active site of thrombin: Phe-Val-Arg, Phe-Pro-Arg and Phe-Pip-Arg (see cols. 2-7). Although calcium ions are needed for thrombin activation, Kakkar et al. do not discuss the subject of making lyophilized preparations of their substrates with or without a calcium salt. That is, Kakkar et al. do not address the alleged distinction between the claimed invention and the assay reagents and method of Váradi et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is (571)272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652

/Andrew Wang/
Supervisory Patent Examiner, Art Unit 1656

rk/2009-05-28